

Understanding Fatigue: The Debilitating Side-effect of Cancer Treatment

Dr Chao-Pin Hsiao

Cancer

UNDERSTANDING FATIGUE: THE DEBILITATING SIDE- EFFECT OF CANCER TREATMENT

Cancer comes with many symptoms, but its life-saving treatments also cause negative side effects. One of these is radiation-induced fatigue, a clinical subtype of cancer-related fatigue and a debilitating issue that causes extreme lack of energy in those receiving radiation therapy. While this is a well-known effect of the treatment, exactly why it happens is unclear. **Dr Chao-Pin Hsiao** at Frances Payne Bolton School of Nursing in Case Western Reserve University, Ohio, is studying the molecular and genetic-level mechanisms that drive fatigue induced by cancer/cancer treatments. Her work on finding fatigue biomarkers provides promise for future combative therapies.

Cancer-related Fatigue

A common and challenging side-effect of cancer and its treatments is fatigue. Known as cancer-related fatigue, this feeling of extreme lack of energy and tiredness can be acute and last a month or less, or chronic, creating a long-lasting impact. Whereas fatigue in a healthy person is caused by activity and relieved by rest, cancer-related fatigue does not follow these patterns and its persistence is emotionally draining.

This health issue can affect all aspects of a person's life, as even the seemingly most simple of activities become difficult. Walking short distances, minor physical actions, thinking clearly and memory can all be negatively impacted, resulting in a diminished quality of life. Even after cancer treatment has ended, the fatigue and its consequences may remain.

One frequently used approach is radiation therapy, and this varies depending on the type, location and size of a tumour. It works by sending high doses of either X-ray or gamma

radiation directly to the tumour, with the aim of killing the cancer cells and shrinking the tumour. The radiation damages the DNA inside the cancer cells beyond repair, which prevents them from repairing themselves and dividing. Eventually, the cells die, are broken down and removed by the body.

Although this is a life-saving technique, it has numerous side effects – many of these are shared across patients, but some are dependent on the location of the tumour and radiotherapy. Nausea, tenderness at the target of radiation, hair loss, skin changes, fertility issues and others can occur during and after treatment. However, one of the most common and severe implications of radiotherapy is radiation-induced fatigue, a type of cancer-related fatigue.

Even though the symptoms of fatigue in cancer are well-documented, it is not entirely clear why they occur. Investigating the molecular and genetic-level mechanisms of radiation-induced fatigue in prostate cancer patients is the work of Dr Chao-Pin Hsiao. She carries out her studies at the Frances



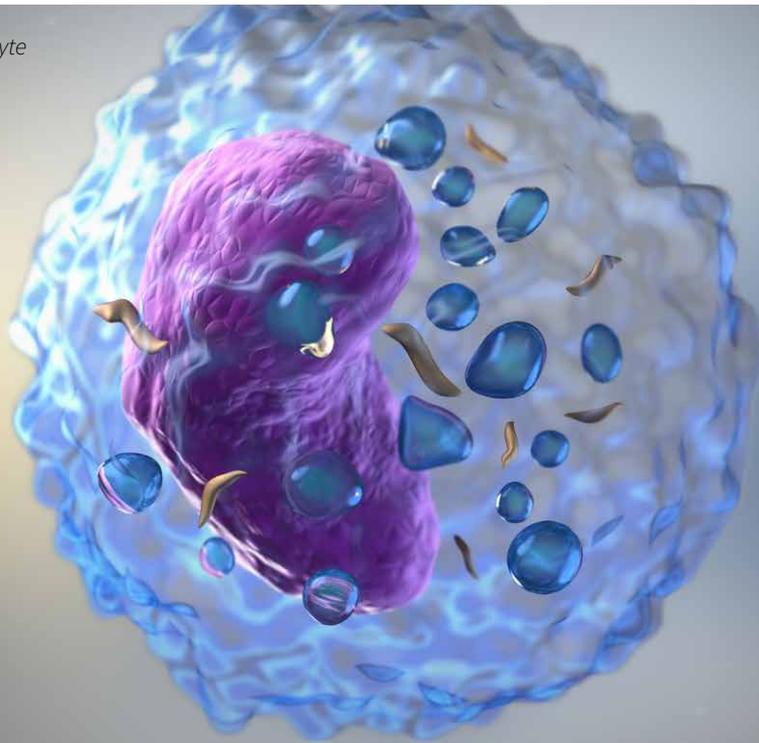
Radiation therapy

Payne Bolton School of Nursing in Case Western Reserve University, Cleveland, Ohio, where she is also an Associate Professor.

The Role of the Mitochondria

In order to understand Dr Hsiao's research, first we need to get to grips with a key component of the cell known as the mitochondria. Often called the 'powerhouse' of the cell, these organelles (structures with a function in a cell) are bound by two membranes. These membranes are a vital component in the role of the mitochondria – to make energy in the form of adenosine triphosphate (ATP) from the food we eat.

Illustration of a lymphocyte



This conversion occurs via a series of biochemical reactions called the Krebs cycle, or the citric acid cycle. The whole process is known as oxidative phosphorylation and once it is complete, the ATP that is produced can be used to power the body or be stored for later in times of energy deficit. In addition to its function of energy production, mitochondria also play a part in normal cell death, calcium storage and heat production.

Dr Hsiao focuses much of her work on the role of the mitochondria in radiation-induced fatigue and she is uncovering how its molecular and genetic mechanisms are involved. Because the radiation causes planned damage to cells, the result is tumour shrinkage, but this is in addition to other damage that results in the side-effects.

Mitochondrial Genes and Fatigue

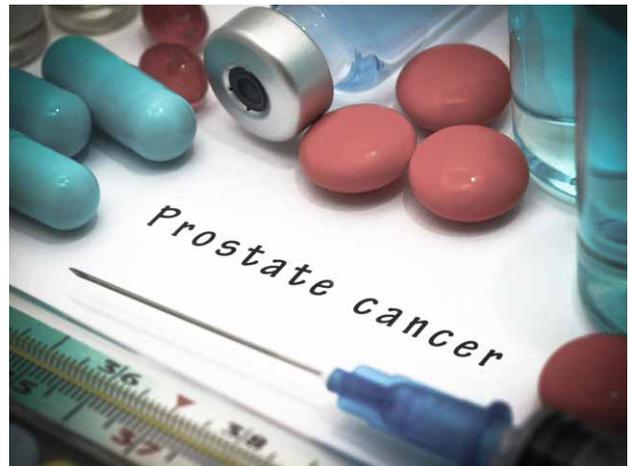
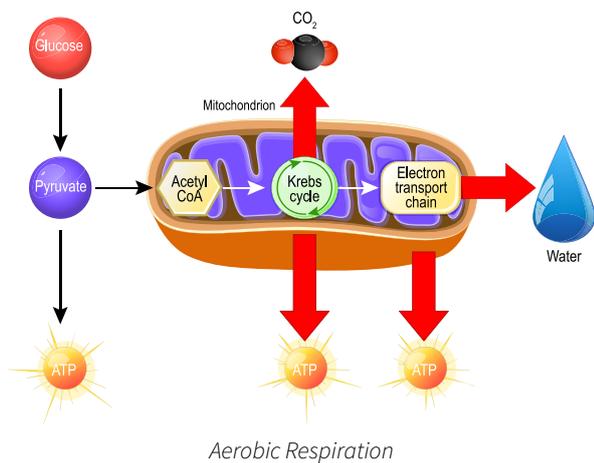
Some of this damage results in the instability of the genome (the complete set of DNA) and inflammation which results in the production of reactive oxygen species that cause further DNA damage. The radiation also impacts the normal jobs of the mitochondria and inhibits its respiratory chain that facilitates energy production.

In an early study, Dr Hsiao studied these biological markers in relation to radiation-induced fatigue in men with prostate cancer receiving a type of radiotherapy called external beam radiation therapy (EBRT). She looked into the genes that are involved in creating new mitochondria (mitochondrial biogenesis) and energy production (bioenergetics). After taking blood samples from the participants, she could decipher which genes were expressed (activated) in ways different than normal during fatigue.

Interestingly, she discovered that specific 14 genes involved in mitochondrial biogenesis and bioenergetics were differentially expressed during radiation therapy and of these, four were significantly related to fatigue. One of these is called BC1 (ubiquinol-cytochrome c reductase) synthesis-like (*BCS1L*) and Dr Hsiao is now delving deeper into the 'how and why' this takes place with the goal of eventually developing effective therapies for managing fatigue. Additional research from her team looked further into the role of incorrectly functioning mitochondria in radiation-induced fatigue. More specifically, they looked at faulty mitochondrial bioenergetics. In a similar format to the previous study, prostate cancer patients were scored on their fatigue level and blood samples were taken at three points during their radiation treatment.

Again, Dr Hsiao honed in on the *BCS1L* gene and these results helped to form a new hypothesis. This is that reduced *BCS1L* (gene/protein) impacts the respiratory chain in the mitochondria. The series of reactions in energy production requires certain proteins in an electron transport chain and when *BCS1L* is in short supply, one of these proteins called complex III is affected. The Rieske iron-sulfur protein is unable to be incorporated into complex III as normal and this results in diminished oxidative phosphorylation and ATP production. Thus, reduced ATP means less energy and more fatigue.

Dr Hsiao believes these findings have the potential to identify novel targets for pharmacological therapeutics but may also be useful for nutritional therapies, known as nutraceutical interventions, to eventually treat fatigue-induced by cancer.



Improving Techniques and Understanding

Working with Dr Leorey Saligan at the National Institute of Nursing Research during her fellowship, Dr Hsiao studied another group of prostate cancer patients, 20 of whom were receiving EBRT and 20 who were on active surveillance who acted as controls between 2010 and 2012. All men were tested for their level of fatigue using a system called Functional Assessment of Cancer Therapy-Fatigue (FACT-F). Those receiving radiation therapy were assessed before, during and at the end of their treatment.

At each of these time points, the participants also had blood taken to test for the expression of genes of interest. The FACT-F scores of radiotherapy patients and controls were no different at the start, however, they decreased at the midpoint for those on treatment and even further at completion. This reducing score indicated worsening fatigue over the treatment time. The blood samples revealed 42 genes that had altered expression during fatigue. Most significantly, a gene called MSA41 was downregulated, meaning its function was minimised.

This gene is involved in the formation of B-cells – important components of the immune response. Therefore, these results indicate that fatigue during radiotherapy may be related to the downregulation of MSA41 and the consequent impairment of the B-cell immune response.

In order to better understand these processes, Dr Hsiao and her team set out to improve the method of obtaining and analysing B-cells from the blood. B-cells are a type of white blood cell called a lymphocyte which is in the family of peripheral mononuclear cells (blood cells with a round nucleus). And like other cells, mononuclear cells rely on the mitochondria for energy. Their new protocol allowed them to look at integrative mitochondrial function, or specific dysfunction, and the individual complex activity of its electron transport chain during oxidative phosphorylation.

Using this improved technique, Dr Hsiao took peripheral mononuclear cells at three time points from a group of patients with prostate cancer, some receiving radiation therapy and

others on active surveillance. She used these cells to determine their mitochondrial oxidative phosphorylation (energy production), electron-transport chain complexes activity, and expression level of *BCS1L* gene and protein. At the same time points, she measured the patients' fatigue on the Piper Fatigue Scale.

In line with her previous studies, Dr Hsiao found significantly worse fatigue in those receiving radiation therapy and related downregulation of *BCS1L*, reduced complex III activity and reduced oxidative phosphorylation. The more severe the downregulation of *BCS1L*, the more a patient suffered from radiation-induced fatigue.

This interesting result suggests that *BCS1L* and complex III in mononuclear cells could be important biomarkers, meaning they indicate how the body responds to a disease or treatment. Therefore, they could be promising targets for future remedies against radiation-induced fatigue.

Mitochondrial Bioenergetic Markers of Cancer-related Fatigue

In one of her most recent studies, Dr Hsiao continued to search for evidence of bioenergetic biomarkers for cancer-related acute and chronic fatigue. Again, she focused on the relationships between a messenger RNA (mRNA) and the protein of *BCS1L*, mitochondrial bioenergetics (oxidative phosphorylation, complex III activity, ATP and reactive oxygen species generation), and fatigue symptoms induced by cancer and cancer treatments. This work led Dr Hsiao to believe that *mBCS1L* and complex III activity are indeed bioenergetic markers for radiation-induced fatigue and therefore, may also be therapeutic agents.

Dr Hsiao's dedicated research into the debilitating fatigue that often goes hand-in-hand with cancer and its treatments shows how understanding its molecular and genetic-level mechanisms is vital. As a result of her work, we now have promising new avenues to explore in the development of potential therapies to ease the suffering of patients undergoing life-saving cancer treatment.



Meet the researcher

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Dr Chao-Pin Hsiao received her undergraduate and master's degrees in nursing from the National Taiwan University and then achieved a PhD in oncology nursing from the University of Arizona in the USA. She went on to complete postdoctoral and research fellow positions at the Symptoms Biology Unit of the National Institute of Nursing Research, the National Institutes of Health in Maryland. Dr Hsiao has held several research and teaching positions and now serves as an Associate Professor at Frances Payne Bolton School of Nursing, Case Western Reserve University in Cleveland, Ohio. Here, she carries out her research into the molecular and genetic mechanisms of mitochondrial bioenergetics in cancer-related fatigue.

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FURTHER READING

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